Chapter 7

Quality of life after hyperthermic isolated limb perfusion for locally advanced extremity soft tissue sarcoma

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Abstract

Background: Quality of life (QoL) and post traumatic stress symptoms (PTSS) were studied in patients with soft tissue sarcoma (STS) of the extremities treated with isolated limb perfusion (ILP), delayed resection with or without adjuvant irradiation.

Methods: Forty-one patients received a questionnaire including the Rand-36 and Impact of Event Scale (IES).

Results: 39 STS survivors, 16 male (41%) and 23 (59%) female, median age 59 (range 15-78) years participated in the questionnaire survey (response rate 95%). Median age at perfusion was 49 (range 14-72) years. No significant differences were found in mean scores between STS survivors and the reference group with the exception of a worse physical functioning. Amputated patients showed significantly worse physical and social functioning, and more role limitations than patients whose limbs were saved. Eleven patients (28%) had a PTSS score of zero, 8 patients (20.5%) had a score $\geq$ 26 suggesting the need for psychological counselling. None of these 8 patients had lost their limb. Patients who indicated that the choice of treatment was made by the surgeon rather than collaboratively showed significantly decreased social functioning, more role limitations and intrusion. Greater treatment satisfaction was significantly related to better social functioning, more vitality, better general health perception, less intrusion, avoidance, and total IES.

Conclusions: Even though STS-survivors' QoL was only different from a reference group in physical functioning, one fifth of the patients suffered from PTSS. An amputation, the physicians' decision rather than the patients' decision for the perfusion treatment and a low satisfaction with the performed treatment negatively influenced QoL.

Introduction

For decades soft tissue sarcomas (STS) were known for their poor long-term outcome with respect to local tumor control, survival as well as functional outcome. Developments in diagnostic imaging and surgical treatment with adjuvant radiotherapy are the cornerstones of the evolution over the past thirty years. Nowadays, STS patients have 5-year survival rates of 60-70%.[1,2] For patients with primarily irresectable locally advanced STS, the so-called hyperthermic isolated limb perfusion (ILP) with Tumor Necrosis Factor alpha (TNFα) and Melphalan, became available in the early nineties with a limb salvage rate of 82%.[3] Survival of extremity-STS-patients is not influenced by limb salvage procedures.[4]

The limb salvage treatment of STS with ILP is a combined modality treatment of regional chemotherapy followed by delayed extensive surgical resections with or without surgical reconstructions and/or adjuvant high dose radiation therapy sometimes followed by systemic chemotherapy with curative or palliative intent. ILP treatment is time consuming and has an uncertain outcome. The risk of loosing a limb after limb salvage procedure is determined by the risk of perioperative complications, local recurrences, and short and long-term treatment induced morbidity.

Patients who are alive after treatment for a potential fatal disease are often analyzed in terms of overall and disease free survival. However, less attention is paid to their quality of life (QoL) in these years gained. Health is defined by the WHO as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. Medical oncologists were one of the first physicians to implement QoL measurements into practice as the question raised to which extent quantity of life was gained at the expense of quality of life.[5] The need to investigate the QoL and the psychological consequences of this combined treatment became increasingly clear as more patients with extremity STS became long-term survivors. It is often hypothesized that for many people with cancer, the survivor advantages of the intensive treatment far outweigh the potential long-term side effects.[6] Findings in the literature are inconsistent concerning that matter: worse, equal or even better QoL in cancer survivors than in healthy comparison group have been reported.[7,8] However, specific subgroups at risk for a worse QoL have been identified such as survivors who are single, less educated, less involved in decision making or less satisfied with the received medical treatment.[9,10] Little is known about the QoL of patients with locally advanced, primary irresectable STS of a limb who underwent a TNF based ILP as an intentional limb saving treatment.

The present study was conducted to gain insight into the QoL in this intensively treated group of patients and into aspects possibly affecting these patients' QoL. The study investigates if STS-survivors differ in QoL from a reference group and evaluates if QoL and stress response symptoms in STS-survivors are related to A) socio-demographic aspects (sex, age, education level, employment and marital status and to B) disease- (time period since perfusion, limb survival, local recurrence, presence of metastases, co-morbidity) and treatment-related aspects (i.e., involvement in the choice of treatment, satisfaction with treatment).

Methods

Procedure and patients

All patients with locally advanced STS who underwent ILP with TNFα and melphalan and an intentional limb salvage treatment during the time period 1991-2003 were eligible for the study. None of the patients had metastases at the time of the ILP treatment. Patients who were alive received a letter explaining the aim of the study, an invitation to participate in the questionnaire survey and a prepaid return envelop.

All patients underwent a complex diagnostic and therapeutic pathway. Before treatment started the option of amputation or an intentional limb saving treatment with ILP was discussed. This study focuses on the STS patients who received the intentional limb saving tumor treatment. The affected limb received an ILP with TNFα and Melphalan followed by delayed resection The technique is described previously.[11] Most patients received adjuvant radiotherapy (60-70 Gy).[11] During the whole range of the intentional limb saving procedure it was possible that patients still lost their limb due to irresectability, vascular complications, wound healing disturbances or radiation induced complications.[3] The TNFα based ILP-containing treatment and the series of patients were recently extensively described.[3,11] All patients were treated following the institutional guidelines.

Measurements

Socio-demographic (sex, age, education level, employment and marital status) and disease related data (time period since perfusion, limb survival, local recurrence, presence of metastases at the time of questionnaire completion, co-morbidity) were assessed from all patients.

On a five options scale, patients could fill in their perception of actual involvement in the decision for treatment. Answers ranged from the doctor only (1) to the doctor and myself in

equal extent (3) to me only (5).[12] In addition patients were asked to score their satisfaction with treatment received on a five-point scale from 'very good' to 'very bad'. Patients were invited to indicate reasons for satisfaction and for dissatisfaction.

Health related quality of life was investigated with a Dutch-language version of the Rand 36[13], a multidimensional self-report questionnaire identical to the Short Form (SF)-36[14] but using a different scoring method. The Rand 36 consists of the following domains: physical functioning (10 items), social functioning (two items), role impairment due to physical problems (four items), role impairment due to emotional problems (three items), mental health (five items), vitality (four items), pain (two items), general health perception (five items) and health change (one item). After recoding and transformation, scores on the subscales could range from 0 to 100. Higher scores indicate a better QoL. Internal consistency of the subscales for the respondents in the present study was good (alpha ranged from 0.70 to 0.92). Normative data are available for the healthy Dutch population. The normative data compromise the mean scores of a group of 1063 men (35%) and women (65%) from a random sample of the population register of a municipality in the Netherlands (number of inhabitants = 108 000). The mean age of the persons in the total random sample was 44 (range 18-89) years.[13]

Post traumatic stress symptoms (PTSS) were measured with the Dutch version of the Impact of Event Scale.[15,16] This scale is often used in studies on cancer patients.[17] In this study information was obtained about the degree to which confrontation with the treatment for a sarcoma was influencing the current daily life of the respondent. Fifteen items measured intrusion (intrusively experienced ideas, images, feelings or bad dreams about the event) (7 items) and avoidance of unpleasant feelings or memories of the event (8 items) using the answer categories: not at all (0), rarely (1), sometimes (3) and often (5). (Intrusion: range 0-35, avoidance: range 0-40) Items of the two subscales are summed to compute a total score. (range 0-75) A total score of more than 26 is a strong indication of clinically significant PTSS, for which psychological help is recommended. Internal consistency of this questionnaire was good (alpha was 0.84 for intrusion, 0.76 for avoidance, and 0.85 for the total IES score).

Statistics

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 12.0; SPSS INC., Chicago, IL). Unpaired t-tests were computed to compare STS-survivors with the reference group in the domains of quality of

life. Pearson correlations, unpaired T-tests, and non-parametric Mann-Whitney and Kruskal-Wallis tests were conducted to examine effects of socio-demographics and treatment- and disease related variables on the outcome measures.

Correlation coefficients < 0.30 indicate a weak association, those between 0.30 and 0.50 a moderately strong association and those > 0.50 a strong association.[18]

Results

Forty-one of the 73 patients (57%), who had been treated with intentional limb salvage procedure for locally advanced, irresectable STS at the Department of Surgical Oncology at the UMCG since 1991 were still alive. Thirty nine patients, 16 male (41%) and 23 (59%) female, median age 59 (range 15-78) years participated in the questionnaire survey (response rate 95%). Median age at perfusion was 49 (range 14-72) years. Median time since perfusion was 7 (range 1-13) years. A fifth of the patients had completed primary school only and only one patient had a university degree. The median education level was lower secondary school. A little over one third of the patients had a job and one third was retired. Over two third of the STS-survivors was married or cohabiting (69%). (Table 1).

Successful limb salvage was achieved in 30 patients, while 9 patients underwent an amputation of the affected limb. Amputation of the affected limb was due to massive necrosis after ILP, local recurrence or critical leg ischemia.[3] The decision to amputate was not influenced by the presence of metastases. At the time of the present study, 4 of the 9 patients (44%) whose limb was amputated had metastases. Of the 30 patients whose limb was saved, 6 patients (20%) had metastases at the time of questionnaire completion. Thirty-three patients had a sarcoma in the lower limb (31% thigh, 21% knee and 33% lower leg) and 6 in the upper limb (15%). Three patients had local recurrence and 10 patients had distant metastases at the time of filling in the questionnaire (Table 1). The vast majority did not suffer from comorbidity.

Nine patients responded that the choice was made by the physician alone and two patients indicated that the choice was made by themselves. Almost half of the patients judged that the physician mainly made the choice of treatment with their participation. Thirty patients were very or rather satisfied with the treatment, 3 patients were not, and 6 scored the answer as neutral. Involvement in treatment choice and satisfaction with treatment were not significantly related. (Table 2).

Table 1 Socio-demographic and disease related characteristics

	N	%
Sex		
Male	16	41
Female	23	59
Age		
Median 59 years		
(range 15-78) years		
Highest education completed		
Primary school	8	21
Lower vocational degree	3	8
Lower secondary school	9	23
Middle secondary school	6	15
High secondary school	4	10
High vocational degree	8	21
University	1	2
Employment		
Paid job	13	33
Voluntary job	2	5
Housekeeping	8	21
Retired	12	31
Student	1	2
Unemployed	3	8
Marital status		
Single/divorced/widowed	12	31
Married/cohabiting	27	69
Location of STS		
Upper limb	6	15
Lower limb	33	85
Limb Survival		
No	9	23
Yes	30	77
Local recurrence		
No	32	82
Yes	3	8
Unknown	4	3
Metastases		
No	29	74
Yes	10	26
Comorbidity		
No	35	90
Yes	4	10

Independent t-tests showed no significant differences in mean scores between the STS survivors and the reference group in most aspects of QoL, except in physical functioning ($p<0.001$) and role limitations due to physical problems ($p=0.01$). A tendency for a worse social functioning was found ($p=0.09$) (Table 3). Eleven patients (28%) had a total stress response symptom score of zero. Eight patients (20.5%) had a score $\geq$ 26 suggesting that psychological counselling was needed.

No significant differences were found between male and female patients in QoL and PTSS. Younger STS-survivors scored better on physical functioning than older ones ($r=-0.34$, $p=0.035$). Educational level was not significantly related to QoL and PTSS in STS patients.

Table 2 Treatment choice and satisfaction and relationship between the two variables.

	Frequency	%
Choice of treatment made by…		
physician only	9	23
mainly physcian	19	49
physician and patient equally	6	15
mainly patient	3	8
patient only	2	5
Satisfaction with treatment		
Very satisfied	20	51
Rather satisfied	10	26
Neutral	6	16
Rather unsatisfied	1	2
Very unsatisfied	2	5
Correlation coefficient*	r=-.19	not significant

* correlation coefficient between the choice of treatment and satisfaction with treatment

Table 3 Quality of life of STS-survivors who underwent ILP and a reference group and comparison between the two groups.

QoL	STS Survivor Mean (SD)	Reference group Mean (SD)	t	p
-Physical functioning	55.6 (30.0)	81.9 (23.2)	-5.42	<.001
-Social functioning	79.8 (25.1)	86.9(20.5)	-1.75	0.09
-Role limitations- physical	61.6 (41.4)	79.4(35.5)	-2.62	0.01
-Role limitations- emotional	87.0 (26.8)	84.1(32.3)	0.63	0.53
-Mental health	76.7 (16.4)	76.8 (18.4)	-0.04	1
-Vitality	64.6 (18.9)	67.4 (19.9)	-0.90	0.37
-Pain	82.2 (21.2)	79.5 (25.6)	0.78	0.44
-General health perception	69.1 (19.1)	72.7 (22.7)	-1.13	0.26
-Health change	57.1 (25.6)	52.4 (19.4)	1.14	0.26
Stress response	**Mean (SD)**			
-Intrusion	6.9 (7.1)			
-Avoidance	5.3 (6.7)			
-Total	12.2 (13.1)			

There was a significant difference in only one domain of QoL when patients employed for wages were compared with the rest: they suffered from significantly less pain (Mann-Whitney U test= -2.47, p= 0.014). Having or not having a partner did not affect functioning in STS survivors. A Mann-Whitney test showed that those whose limb was amputated reported significantly worse physical (U=-2.41, p=0.016) and social functioning (U=-2.27, p=0.023), and they reported more role limitations due to physical (U=-2.39, p=0.017) and emotional (U=-2.45, p=0.014) problems than those whose limb could be saved. No significant

differences were found in mental health, vitality, pain, general health perception and avoidance, intrusion and total IES between the two groups. No significant relationships were found between time since initial treatment and the various QoL domains and PTSS.

If patients had metastases at the time of the survey, they reported significantly worse physical functioning (U=-2.13, p=0.034), and more role limitations due to physical (U=-2.14, p=0.032) and emotional (U=-2.92, p=0.004) problems. There were no differences in the other areas of QoL nor in intrusion, avoidance and total stress response symptoms. None of the nine amputated patients had a score $\geq$ 26 on the total IES. Of the ten patients with metastases two had a score $\geq$ 26. The effects of incidence of local recurrence and chronic diseases on QoL and STS could not be examined because only a few patients had experienced local recurrence (n=3) or suffered from co-morbidity (n=4).

Kruskal Wallis tests showed that those who were less involved in the decision for treatment had significantly higher scores on intrusion (Chi-square=11.37, p=0.023). Also, they tended to report more total IES (Chi-square=9.12, p=0.058) and a worse social functioning (Chi-square=9.17, p=0.057). Greater treatment satisfaction was related to a better social functioning (r=-0.36; p=0.024), more vitality (r=-0.32; p=0.046), and a better general health perception (r=-0.36; p=0.028). Higher treatment satisfaction was significantly associated with less intrusion (r=0.57; p<0.0001), avoidance (r=0.35; p=0.27) and total IES (r=0.58; p<0.0001). These correlation coefficients ranged from moderately strong to strong.

Fourteen patients (36%) indicated additionally why they were satisfied with the treatment, 18 (46%) why treatment had discouraged them, and 7 patients (18%) mentioned both positive and negative aspects of treatment. Positive experiences mentioned by 16/21 of the patients were that they were satisfied with the final result and the fact that the course of treatment was as explained and therefore expected. The remaining 5/21 mentioned they experienced the treatment positively because they had expected worse and because they had suffered little pain. Discouraging arguments mentioned were the intensity of treatment (20/25), long recovery period (9/25) and/or the fact that they had been seriously ill as a consequence of the treatment (6/25).

Discussion

The aim of the current study was to gain insight into the QoL and PTSS of patients with locally advanced, primary irresectable STS of a limb who underwent an intensive and extensive sarcoma treatment that consisted out of a TNFα based ILP followed by delayed

surgical resection ± adjuvant high dose external beam radiotherapy as an intentional limb saving treatment.

Physical functioning and role limitations due to physical problems were the only domains in which our group of patients scored significantly lower than the reference group. The problems perceived in the physical domains could be explained by the resection of a large muscular compartment and often adherent structures in the affected part of the limb that the sarcoma patients had undergone. Obviously, such invasive surgery affects the physical functioning of these sarcoma patients. On the other hand, functioning in the remaining QoL domains in these patients was the same as in the reference group. It has been suggested that patients with cancer seem to change their internal standards and their expectations about life during treatment. Other studies also postulate that cancer patients evaluate QoL according to their new expectations and different standards.[5,19] The limitations patients experienced in physical functioning do not seem to affect functioning in the other QoL domains.

The finding of a surprisingly high percentage of 20.5% of the patients having clinically elevated PTSS is in contrast to literature showing a prevalence of clinically high PTSS among people with cancer varying from 3% to 12% depending on the cancer treatment.[20-23] The 20.5% PTSS rate found is this study is comparable with more traditional traumatic events such as rape, war, disaster and accidents in general samples.[21]

To distinguish those in our group of patients who had more problems concerning QoL and PTSS, we investigated the effects of socio-demographic, disease and treatment related variables.

Socio-demographics

Younger STS-survivors scored better on physical functioning than older STS-survivors. Some other QoL studies also showed that the physical autonomy score was affected by age.[24,25] In the other QoL domains and PTSS we found no associations with age. This is in contrast with the literature reporting that younger age is a risk factor for psychosocial distress, anxiety and depressive symptoms among cancer survivors.[19,26]

Other socio-demographics such as sex, education level, marital status were not related to QoL and PTSS in our studies. This is different from findings in literature that show that women tend to develop somatic complaints more quickly after negative life events[24,27]; a higher educational level is associated with a higher QoL in the general population[19,24]; and that having a partner has been identified as a predictor of better well-being in the general population, in particular in men.[19,26] There was a significant difference in one domain of QoL

when patients employed for wages were compared with the rest: they suffered from significantly less pain. This can be a chance finding. Another suggestion is that work distracts and reduces pain sensation. More research is needed to evaluate this finding.

Illness related

Patients with an amputated limb had a worse QoL score in physical and social functioning, and in role limitations due to physical and emotional problems. This is in contrast with the literature that showed no differences in QoL between patients whose limb was amputated and patients treated with conservative surgery and adjuvant radiation treatment.[28-30] These studies, however, describe patients who were randomised between amputation and limb saving treatment. In our group, all treatments started intentionally with a limb-saving purpose. Our results suggest that once the patients are on the pathway where limb-saving treatment seems possible, an eventual amputation actually may make a difference resulting in a decreased perception in some of the QoL domains.

Even though more quality of life problems were found in patients whose limb was amputated it appeared that none of these patients had a posttraumatic response symptom score indicative of need of professional psychosocial care. A hypothesis for this phenomenon may be that the loss of a limb has released patients from the insecurity of a possible loss in the future. The threat of local recurrence and further damage to the limb due to long-term effects of radiation or vascular incompetence may be like a sword above the head that may fall at any moment. An equal percentage of patients with metastasised disease had a clinically elevated PTSS score as found in the complete study group (20%). Metastasised patients did have problems in physical functioning and role limitations due to physical and emotional problems.

We found no effect of time in relation to QoL suggesting physical functioning problems are of a more permanent nature. In Lamperts study patients with lower extremity STS were more at risk to become disabled than patients with STS in other areas of the body.[31] In our own data the number of upper extremity STS patients (n=3) was too small to detect significant differences in QoL and PTSS compared to patients whose affected limb was a lower extremity.

Choice of treatment

This study shows that those patients who indicated that the surgeon made the treatment choice rather than they themselves, showed a decreased social functioning, more role limitations due to physical problems and higher levels of intrusion. This is in agreement with other studies

reporting that patients benefit from participating in medical decision making.[10] Despite all the reasonable doubts patients may have, it seems important that the patient is at least involved in the final decision for his or her treatment. Other studies also mention that patients who perceive that they have decisional control in their treatment may regain control-perception over the disease as well, which may ultimately lead to a higher QoL.[32-36] It may be that greater attention should be paid to the communication of treatment options and its consequences to the patient so that the patient is better able to make an informed decision.

Our results also showed that patients who were more satisfied with treatment reported less PTSS and a better QoL, a finding in line with earlier research.[10,37-40] In contrast to other studies no significant relationship was found between decision involvement and treatment satisfaction in the current study.[10,39]

In the light of data indicating that 20.5% of the STS survivors experience PTSS symptoms even years after treatment and that patients, in particular those whose limb was amputated, had problems in the physical QoL domains, identifying ways to prevent or relieve these symptoms should be considered. A suggestion would be a multimodal rehabilitation program including a physical and a psychosocial program that might help reduce the problems in the physical domains and the psychosocial distress in these patients. An intensive multi-focus rehabilitation program for cancer patients after completion of their cancer treatment appeared to have immediate and longer term beneficial effects on physiological functioning and quality of life.[41] Furthermore, attention should be paid to the issue of collaborative decision making that may be better achieved with informing the patient more comprehensively about treatment options and possible consequences. Attention to communication issues may also increase patient satisfaction.

The inclusion of a validated generic QoL questionnaire and the high response rate (95%) are the strengths of this study. On the other hand only 41 patients (57%) of the original study population of 73 patients were eligible since the remaining 32 patients were deceased at the time of the survey. In addition, the present study is a retrospective cross-sectional study. The measurement of quality of life in STS patients is a dynamic rather than a static process that requires reassessment. Consecutive quality of life measurements may give insight into change over time and causal relationships between variables.

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